1103326-0557

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED OFFICE (DO/US)

PCT/SE99/00319	04 March 1999	06 Mar. 1998 and 20 Apr. 1998
International Application Number	International Filing Date	Priority Date(s) Claimed

NEW USE
Title of Invention

RAMACHANDRAN, Janakiraman

Applicant(s) for DO/US

"Express Mail" Label No EH 623290917US

Date of Deposit APRIL 14, 1999. I hereby certify that this paper is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above and is addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231

Hector Sanchez
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(Signature of person mailing paper or fee)

BOX PCT
Assistant Commissioner for Patents
Washington, D.C. 20231

To the United States Designated Office (DO/US):

I. Accompanying this transmittal letter are certain items which are required under 35 U.S.C. 371 in order that United States National processing of the above identified International application may commence:

(X) at the expiration of the applicable time limit under PCT Articles 22 and 39(1) according to the provisions of 35 U.S.C. 371(b).

( ) as soon as possible upon receipt of this express request under 35 U.S.C. 371(f).

1. The U.S. National fee [35 U.S.C. 371(c)(1)]

a. ( ) was previously transmitted by applicant on (date)____.

b. ( ) is submitted herewith as follows:

FOR	NO. FILED	NO. EXTRA	SMALL ENTITY RATE	FEE	or	OTHER THAN SMALL ENTITY RATE	FEE
Basic Fee	(USPTO NOT ISA OR IPEA)		////	$485	or	/////	**$970**
Total Claims	- 20 =	--	x 9 =		or	x18 =	
Ind. Claims	**2- 3**	--	x39 =		or	x78 =	
(**X**) Multiple Dependent Claim Presented			+130 =		or	+260 =	**260**
	TOTAL NATIONAL FEE		$____		or		$1230

i. ( ) A check in the amount of $_____ is enclosed.

ii. (**X**) Please charge the filing fee, multiple dependent claim fee (if applicable), excess independent claims fee (if applicable), and excess total claims fee (if applicable) to **Deposit Account No. 23-1703**.

iii. (X) The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 23-1703. A duplicate copy of this sheet is enclosed.

(iv) ( ) The filing fee is not enclosed.

2. A copy of the International application as filed [35 U.S.C. 371(c)(2)]:

a. (**X**) is transmitted herewith.

b. ( ) is not required as the application was filed with the United States Receiving Office.

c. ( ) has been transmitted

i. ( ) by the International Bureau. Date of mailing of the application (from form PCT/IB/308): _____ A copy of form PCT/IB/308 is enclosed.

ii. ( ) by applicant on (date) _____.

3. A translation of the International application into the English language [35 U.S.C. 371(c)(2)]:

a. ( ) is transmitted herewith.

b. (**X**) is not required as the application was filed in English.

c. ( ) was previously transmitted by applicant on (date)_____.

4. Amendments to the claims of the International application under PCT Article 19 [35 U.S.C. 371(c)(3)]:

a. ( ) are transmitted herewith.

b. ( ) have been transmitted

i. ( ) by the International Bureau. Date of mailing of the amendments (from form PCT/IB/308): _____.

ii. ( ) by applicant on (date) _____.

c. (**X**) have not been transmitted as

i. ( ) no notification has been received that the International Searching Authority has received the Search Copy.

ii. ( ) the Search Copy was received by the International Searching Authority but the Search Report has not yet issued. Date of receipt of Search Copy (from form PCT/ISA/202): _____.

iii. ( ) applicant chose not to make amendments under PCT Article 19. Date of mailing of Search Report (from form PCT/ISA/210):

iv. (X) the time limit for the submission of amendments has not yet expired. The amendments or a statement that amendments have not been made will be transmitted before the expiration of the time limit under PCT Rule 46.1.

5. A Translation of the amendments to the claims under PCT Article 19 [35 U.S.C. 371(c)(3)]:

a. ( ) is transmitted herewith.

b. ( ) is not required as the amendments were made in the English language.

c. (X) has not been transmitted for reasons indicated at point I.4.b. or c. above.

6. A declaration for patent application of the inventor [35 U.S.C. 371(c)(4)] complying with 35 U.S.C. 115:

a. ( ) was previously submitted by applicant on (date) _____

b. (X) is submitted herewith; and such oath or declaration

i. ( ) are attached to the application.

ii. (X) identifies the application and any amendments under PCT Article 19 which were transmitted as stated in points 1.2.b. or c. and 1.4. and states that they were reviewed by the inventor as required by 37 CFR 1.70.

c. ( ) will be submitted subsequently.

II. Concerning other documents:

1. An International Search Report or Declaration under PCT Article 17(2)(a):

a. ( ) has been transmitted by the International Bureau. Date of mailing (from form PCT/IB/308): _____ A copy of form PCT/IB/308 is enclosed

b. ( ) is not required as the application was searched by the United States International Searching Authority.

c. ( ) A copy of the International Search Report is transmitted herewith.

d. ( ) has been submitted by applicant on (date) _____.

2. A Statement of prior art under 37 CFR 1.97 and 1.98:

a. ( ) is transmitted herewith including copies of the references cited on the attached form PTO-1449. Also included is a copy of the International-Type Search Report issued in the Swedish priority document.

b. ( ) will be transmitted within THREE MONTHS of the date of submission of requirements under 35 U.S.C. 371(c).

c. ( ) was previously submitted by applicant on _____, in application serial no. _____.

3. (**X**) An Assignment is transmitted herewith for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.

a. (**X**) Please charge the $40 assignment recordation fee to Deposit Account No. 23-1703.

b. ( ) A check in the amount of $___ is enclosed.

4. **Other document(s) or information included:**

- Copy of PCT/RO/101 - The PCT Request Form; and
- Copy of PCT/ISA/201/SE - The International-Type Search Report issued in Swedish Appln. 9801370-9, filed April 20, 1998.

Respectfully submitted,

April 14, 1999
DATE

Richard J. Sterner
Reg. No. 35,372

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Patent Department
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enclosures

ASTRA

Applicant: **Astra Aktiebolag**
S-151 85 Södertälje
Sweden

Title: **NEW USE**

Reference: R 1923

Inventors: J. RAMACHANDRAN

February 20, 1998
BAK
R 1923 FF

NEW USE

The present invention relates to the use of certain isatin and oxindole derivatives in the treatment of mycobacterial diseases, particularly those diseases caused by pathogenic mycobacteria such as *Mycobacterium tuberculosis, M. bovis, M. avium* and *M. marinum.*

Tuberculosis is still a major public health problem affecting nearly all parts of the world. Based on skin test reactivity it has been estimated that about one-third of the world's population, i.e., 1.7 billion people, are infected with *Mycobacterium tuberculosis.* Despite the availability of effective chemotherapies, it is responsible for three million deaths and from eight to ten million new cases annually and thus remains the leading cause of death world-wide due to a single infectious agent: 26% of all preventable deaths, 7% of all deaths. According to the World Health Organisation, 450,000 deaths per year due to tuberculosis in developing countries occur in children under fifteen years of age, and the disease mostly affects the younger, more productive adults.

There are five front-line drugs known to be highly effective against *M. tuberculosis* and five second-line drugs that can be used when resistance to one or more of the front-line drugs is detected. The preferred mode of treatment for tuberculosis is the short course chemotherapy in which there are two phases. The first phase consists of a daily regimen for two months with isoniazid (300 mg), rifampicin (600 mg), pyrazinamide (3 g) and ethambutol (1.5 g). The second phase or the continuation phase consists of a daily regimen for the next four months with isoniazid and rifampicin. Although infection with drug-sensitive strains of *M. tuberculosis* can be effectively cured with the short course chemotherapy, the cure rate is very poor in most countries due to poor compliance which is reflective of the long duration of therapy.

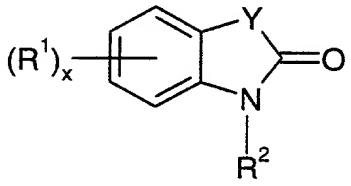
The situation is further complicated by the rapid emergence of multi-drug resistant tuberculosis (MDR-TB) strains. For example, in certain populations, the incidence of resistance to isoniazid is as high as 26% and the resistance to rifampicin is about 15%.

Prior to 1984, about 10% of tubercle bacilli isolated from patients in the United States were resistant to at least one single mycobacterial drug. By 1984, this figure had risen to 52%, of which over half (32%) were resistant to more than one drug (MDR-TB). Ten percent of the recorded MDR-TB cases have occurred in previously healthy people whose mortality rate - 70 to 90% - has been nearly the same as that of immunosuppressed individuals with MDR-TB. The number of cases of MDR-TB has doubled since 1984 and in many of them the tubercle bacilli are resistant to both isoniazid and rifampicin. The median interval between diagnosis of MDR-TB and death is only four weeks and therefore MDR-TB demands a shorter response time between diagnosis and appropriate commencement of treatment. However, MDR-TB is difficult to treat as such since most patients do not respond very well to the second-line drugs and the cost of alternate treatment procedures, including hospitalisation and possibly surgery, increases the cost to as much as ten times the cost of traditional treatment.

Thus, there is an urgent medical need to identify new drugs with significant therapeutic activity against single- or multiple-drug resistant strains of *M. tuberculosis* and with pharmacokinetic properties that permit reduced dosing which will in turn encourage better compliance.

WO 93/12085 and WO 94/29272 describe two classes of isatin and oxindole derivatives which function as acetylcholinesterase inhibitors and which have application as pharmaceuticals in the treatment of cognitive dysfunctions such as Alzheimer's disease, senile dementia, Parkinson's disease, Down's syndrome and Huntington's chorea.

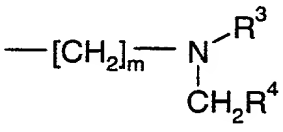
In accordance with the present invention, there is provided the use of a compound of general formula



(I)

wherein x represents 0 or 1, R^1 represents a 3- to 7-membered (hetero)cycloalkyl group or a phenyl group, Y represents a group CH_2 or >C=O, and R^2 represents either a C_1-C_{12} alkyl group optionally substituted by one or more halogen atoms,

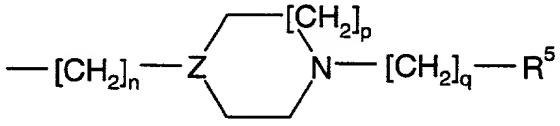
a group



(A)

wherein m represents an integer from 3 to 7, R^3 represents a C_1-C_6 alkyl group and R^4 represents a cyclohexyl or phenyl group optionally substituted by one or more substituents selected from the group consisting of a halogen atom, C_1-C_6 alkyl and C_1-C_6 alkoxy group,

or a group



(B)

wherein n represents an integer from 2 to 4, p and q independently represent an integer from 1 to 2, Z represents N or CH and R^5 represents a cyclohexyl or phenyl group optionally substituted by one or more substituents selected from the group consisting of a halogen atom, C_1-C_6 alkyl and C_1-C_6 alkoxy group,

or a pharmaceutically-acceptable salt or solvate thereof in the manufacture of a medicament for use in the treatment of a mycobacterial disease, in particular tuberculosis.

Preferably Y in formula (I) represents a group >C=O.

Preferably R^1 represents a 5- to 7-membered (hetero)cycloalkyl group (e.g. a cyclopentyl, cyclohexyl, cycloheptyl, pyrrolidinyl, imidazolinyl, pyrazolidinyl, piperidinyl, piperazinyl or morpholinyl group) or a phenyl group. Most preferably R^1 represents a cyclopentyl, cyclohexyl, cycloheptyl or 1-piperidinyl group. Particularly advantageous compounds of formula (I) to use are those in which the group R^1 is located in the 5- or 7-position of the bicyclic ring system.

R^2 represents either a C_1-C_{12}, preferably C_4-C_{12}, alkyl group (e.g. a methyl, ethyl, propyl, butyl, 2-methylpropyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, undecyl or dodecyl group); a group (A) as defined above in which m represents an integer from 3 to 7, preferably 4 or 5, R^3 represents a C_1-C_6 alkyl group (e.g. a methyl, propyl, butyl, pentyl, hexyl or especially ethyl group) and R^4 represents a cyclohexyl or, preferably, phenyl group optionally substituted by one or more, e.g. one, two, three or four, substituents selected from the group consisting of a halogen atom (e.g. fluorine, chlorine or bromine), C_1-C_6 alkyl (e.g. methyl, ethyl or propyl) and C_1-C_6 alkoxy (e.g. methoxy, ethoxy or propoxy) group; or a group (B) as defined above in which n represents an integer from 2 to 4, preferably 2, p and q independently represent an integer of 2 or preferably 1, Z represents N or CH and R^5 represents a cyclohexyl or, preferably, phenyl group optionally substituted by one or more, e.g. one, two, three or four, substituents selected from the group consisting of a halogen atom (e.g. fluorine, chlorine or bromine), C_1-C_6 alkyl (e.g. methyl, ethyl or propyl) and C_1-C_6 alkoxy (e.g. methoxy, ethoxy or propoxy) group.

In the present invention, it is preferred to use a compound being:
5-Cyclohexyl-1-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-1H-indole-2,3-dione;
7-Cycloheptyl-1-[2-[4-(phenylmethyl)-1-piperazinyl]ethyl]-1H-indole-2,3-dione;
5-Cyclohexyl-1-(5-(N-ethyl-N-phenylmethylamino)pentyl)-1H-indole-2,3-dione;
5-Cyclohexyl-1,3-dihydro-1-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-2H-indol-2-one;
1-(4-(N-Ethyl-N-phenylmethylamino)butyl)-1H-indole-2,3-dione;
5-Phenyl-1-[2-[4-(phenylmethyl)-1-piperazinyl]ethyl]-1H-indole-2,3-dione;
7-Cyclopentyl-1-[2-[4-(phenylmethyl)-1-piperazinyl]ethyl]-1H-indole-2,3-dione;

5-(1-Piperidinyl)-1-[2-[4-(phenylmethyl)-1-piperazinyl]ethyl]-1H-indole-2,3-dione;

1-(4-Bromobutyl)-5-cyclohexyl-1H-indole-2,3-dione;

1-Nonyl-7-phenyl-1H-indole-2,3-dione;

1-Heptyl-7-phenyl-1H-indole-2,3-dione;

1-Octyl-7-phenyl-1H-indole-2,3-dione;

1-Decyl-7-phenyl-1H-indole-2,3-dione;

1-Undecyl-7-phenyl-1H-indole-2,3-dione;

1-Pentyl-7-phenyl-1H-indole-2,3-dione;

1-Butyl-7-phenyl-1H-indole-2,3-dione;

1-(2-Methylpropyl)-7-phenyl-1H-indole-2,3-dione;

1-Hexyl-7-phenyl-1H-indole-2,3-dione;

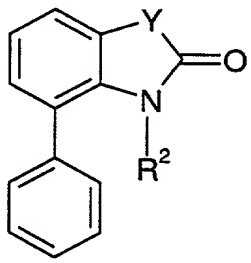
1-Dodecyl-7-phenyl-1H-indole-2,3-dione; or

1-(4-Bromobutyl)-7-phenyl-1H-indole-2,3-dione;

or a pharmaceutically-acceptable salt or solvate thereof.

The compounds of formula I may be prepared by processes known in the art or by processes analogous to those known in the art, for example, as described in WO 93/12085 and WO 94/29272.

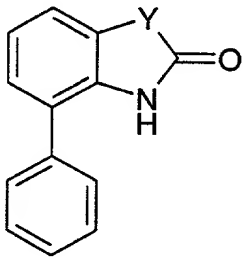
Some of the compounds of formula (I) above are novel. Therefore, the present invention further provides a compound of the general formula



(I')

wherein Y and R^2 are as hereinbefore defined, or a pharmaceutically-acceptable salt or solvate thereof.

The present invention still further provides a process for preparing a compound of formula (I') which comprises reacting a compound of formula



(II)

in which Y is as hereinbefore defined, with a compound of general formula (III), R^2-L, where L represents a leaving group such as a halogen atom and R^2 is as hereinbefore defined, and optionally thereafter forming a pharmaceutically-acceptable salt or solvate thereof.

The process may conveniently be carried out in a solvent such as dimethylformamide or tetrahydrofuran and in the presence of a base such as triethylamine, anhydrous potassium carbonate or sodium hydride. The process will suitably be carried out at a temperature in the range from 0 to 100 °C.

It will be appreciated by those skilled in the art that in the process of the present invention certain functional groups in the intermediate compounds may need to be protected by protecting groups. Thus, the final stage in the preparation of the compounds of formula (I') may involve the removal of one or more protecting groups.

The protection and deprotection of functional groups is described in 'Protective Groups in Organic Chemistry', edited by J.W.F. McOmie, Plenum Press (1973) and 'Protective Groups in Organic Synthesis', 2nd edition, T.W. Greene and P.G.M. Wuts, Wiley-Interscience (1991).

The compounds of formula (I) or (I') may be converted to a pharmaceutically-acceptable salt or solvate thereof, preferably an acid addition salt such as a hydrochloride,

hydrobromide, phosphate, acetate, fumarate, maleate, tartrate, citrate, oxalate, methanesulphonate or *p*-toluenesulphonate, or an alkali metal salt such as a sodium or potassium salt.

Certain compounds of formula (I) or (I') are capable of existing in stereoisomeric forms. It will be understood that the invention encompasses all geometric and optical isomers of the compounds of formula (I) or (I') and mixtures thereof including racemates. Tautomers and mixtures thereof also form an aspect of the present invention.

The compounds according to the present invention are advantageous in that they possess bactericidal activity against mycobacteria, particularly pathogenic mycobacteria such as *Mycobacterium tuberculosis, M. bovis, M. avium* and *M. marinum*. Accordingly, in another aspect, the invention provides a method of treating a patient suffering from, or at risk of, a mycobacterial disease, which comprises administering to the patient a therapeutically effective amount of a compound of formula (I) or (I'), or a pharmaceutically-acceptable salt or solvate thereof, as defined above.

The compounds of formula (I) or (I') and pharmaceutically-acceptable salts and solvates thereof may be used on their own but will generally be administered in the form of a pharmaceutical composition in which the formula (I) or (I') compound/salt/solvate (active ingredient) is in association with a pharmaceutically-acceptable adjuvant, diluent or carrier. Depending on the mode of administration, the pharmaceutical composition will preferably comprise from 0.05 to 99 %w (per cent by weight), more preferably from 0.10 to 70 %w, of active ingredient, and, from 1 to 99.95 %w, more preferably from 30 to 99.90 %w, of a pharmaceutically-acceptable adjuvant, diluent or carrier, all percentages by weight being based on total composition. The pharmaceutical composition may additionally contain another anti-tubercular agent and/or various other ingredients known in the art, for example, a lubricant, stabilising agent, buffering agent, emulsifying agent, viscosity-regulating agent, surfactant, preservative, flavouring or colorant.

Thus, the present invention also provides a pharmaceutical composition comprising a compound of formula (I'), or a pharmaceutically-acceptable salt or solvate thereof, as hereinbefore defined in association with a pharmaceutically-acceptable adjuvant, diluent or carrier.

The invention further provides a process for the preparation of a pharmaceutical composition of the invention which comprises mixing a compound of formula (I'), or a pharmaceutically-acceptable salt or solvate thereof, as hereinbefore defined with a pharmaceutically-acceptable adjuvant, diluent or carrier.

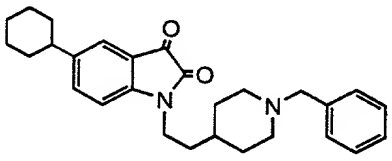
The daily dosage of formula (I) or (I') compound administered will, of course, vary with the compound employed, the mode of administration, the treatment desired and the mycobacterial disease indicated. However, in general, satisfactory results will be obtained when the compound of formula (I) or (I') is administered at a daily dosage not exceeding 1 g, e.g. in the range from 10 to 50 mg/kg body weight.

The compounds according to the invention may be administered systemically, e.g. by oral administration in the form of tablets, capsules, syrups, powders or granules, or by parenteral administration in the form of solutions or suspensions.

The present invention will be further illustrated with reference to the following examples.

Example 1

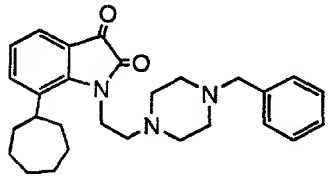
5-Cyclohexyl-1-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-1H-indole-2,3-dione



The title compound was prepared as described in Example 104 of WO 93/12085.

Example 2

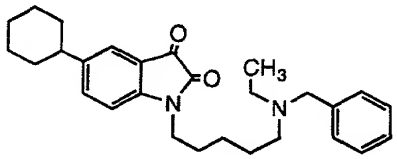
7-Cycloheptyl-1-[2-[4-(phenylmethyl)-1-piperazinyl]ethyl]-1H-indole-2,3-dione



The title compound was prepared as described in Example 63 of WO 93/12085.

Example 3

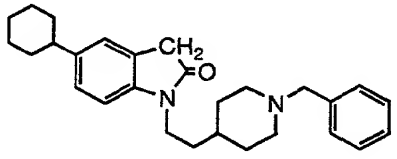
5-Cyclohexyl-1-(5-(N-ethyl-N-phenylmethylamino)pentyl)-1H-indole-2,3-dione



The title compound was prepared as described in Example 22 of WO 94/29272.

Example 4

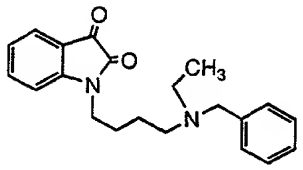
5-Cyclohexyl-1,3-dihydro-1-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-2H-indol-2-one



The title compound was prepared as described in Example 107 of WO 93/12085.

Example 5

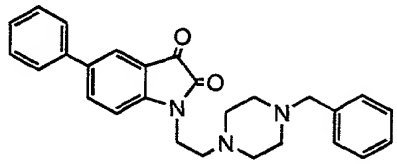
1-(4-(N-Ethyl-N-phenylmethylamino)butyl)-1H-indole-2,3-dione



The title compound was prepared as described in Example 19 of WO 94/29272.

Example 6

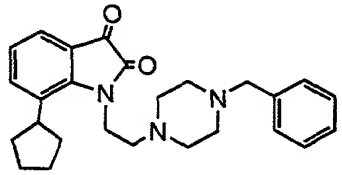
5-Phenyl-1-[2-[4-(phenylmethyl)-1-piperazinyl]ethyl]-1H-indole-2,3-dione



The title compound was prepared as described in Example 97 of WO 93/12085.

Example 7

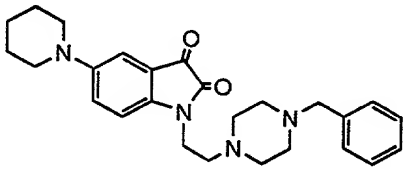
7-Cyclopentyl-1-[2-[4-(phenylmethyl)-1-piperazinyl]ethyl]-1H-indole-2,3-dione



The title compound was prepared as described in Example 61 of WO 93/12085.

Example 8

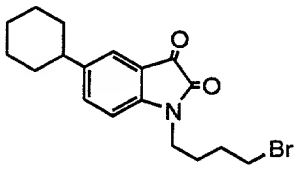
5-(1-Piperidinyl)-1-[2-[4-(phenylmethyl)-1-piperazinyl]ethyl]-1H-indole-2,3-dione



The title compound was prepared in a manner analogous to Example 14 of WO 93/12085 but using 5-(1-piperidinyl)-1H-indole-2,3-dione.

Example 9

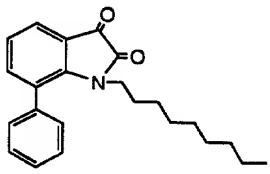
1-(4-Bromobutyl)-5-cyclohexyl-1H-indole-2,3-dione



The title compound was prepared as described in Example 29 of WO 94/29272.

Example 10

1-Nonyl-7-phenyl-1H-indole-2,3-dione

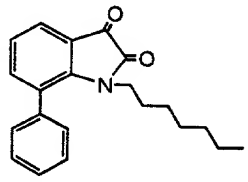


The title compound was prepared in a manner similar to the process step described in the text from Page 7, line 34 to Page 8, line 5 of WO 94/29272 but using a haloalkane such as 1-bromononane together with 7-phenyl-1H-indole-2,3-dione.

^{1}H NMR : δ 0.7 (2H, p), 0.9 (3H, t), 0.9-1.3 (12H, m), 3.4 (2H, dd), 7.1 (1H, t), 7.3-7.5 (6H, m), 7.6 (1H, d)

Example 11

1-Heptyl-7-phenyl-1H-indole-2,3-dione

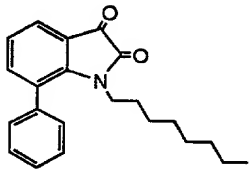


The title compound was prepared as described in Example 10 above except that 1-bromoheptane was used.

^{1}H NMR : δ 0.7 (2H, p), 0.9 (3H, t), 0.9-1.3 (8H, m), 3.4 (2H, dd), 7.1 (1H, t), 7.3-7.5 (6H, m), 7.6 (1H, d)

Example 12

1-Octyl-7-phenyl-1H-indole-2,3-dione

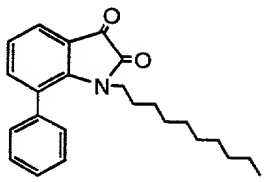


The title compound was prepared as described in Example 10 above except that 1-bromooctane was used.

^{1}H NMR : δ 0.7 (2H, p), 0.9 (3H, t), 0.9-1.3 (10H, m), 3.4 (2H, dd), 7.1 (1H, t), 7.3-7.5 (6H, m), 7.6 (1H, d)

Example 13

1-Decyl-7-phenyl-1H-indole-2,3-dione

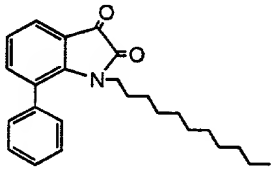


The title compound was prepared as described in Example 10 above except that 1-bromodecane was used.

^{1}H NMR : δ 0.7 (2H, p), 0.9 (3H, t), 0.9-1.3 (14H, m), 3.4 (2H, dd), 7.1 (1H, t), 7.3-7.5 (6H, m), 7.6 (1H, d)

Example 14

1-Undecyl-7-phenyl-1H-indole-2,3-dione

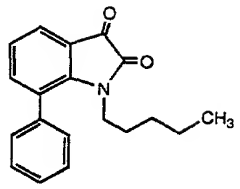


The title compound was prepared as described in Example 10 above except that 1-bromoundecane was used.

^{1}H NMR : δ 0.7 (2H, p), 0.9 (3H, t), 0.8-1.3 (16H, m), 3.3 (2H, dd), 7.1 (1H, t), 7.3-7.5 (6H, m), 7.6 (1H, d)

Example 15

1-Pentyl-7-phenyl-1H-indole-2,3-dione

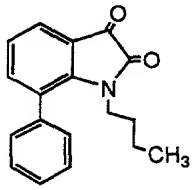


The title compound was prepared as described in Example 10 above except that 1-bromopentane was used.

^{1}H NMR : δ 0.6-0.8 (5H, m), 0.9-1.1 (2H, m), 1.1-1.3 (2H, m), 3.4 (2H, dd), 7.1 (1H, t), 7.3-7.5 (6H, m), 7.6 (1H, d)

Example 16

1-Butyl-7-phenyl-1H-indole-2,3-dione

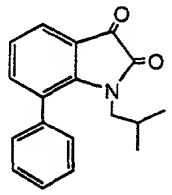


The title compound was prepared as described in Example 10 above except that 1-bromobutane was used.

^{1}H NMR : δ 0.6 (3H, t), 0.7-0.8 (2H, m), 1.1-1.3 (2H, m), 3.3 (2H, dd), 7.1 (1H, t), 7.3-7.5 (6H, m), 7.6 (1H, d)

Example 17

1-(2-Methylpropyl)-7-phenyl-1H-indole-2,3-dione

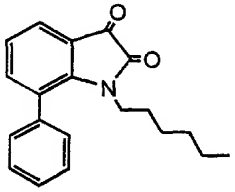


The title compound was prepared as described in Example 10 above except that 1-bromo-2-methylpropane was used.

^{1}H NMR : δ 0.5 (6H, d), 1.3-1.5 (1H, m), 3.2 (2H, d), 7.1 (1H, t), 7.3-7.5 (6H, m), 7.6 (1H, d)

Example 18

1-Hexyl-7-phenyl-1H-indole-2,3-dione

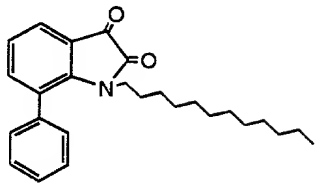


The title compound was prepared as described in Example 10 above except that 1-bromohexane was used.

^{1}H NMR : δ 0.6-0.7 (2H, m), 0.7 (3H, t), 0.8-1.0 (2H, m), 1.0-1.2 (4H, m), 3.3 (2H, dd), 7.1 (1H, t), 7.3-7.5 (6H, m), 7.6 (1H, d)

Example 19

1-Dodecyl-7-phenyl-1H-indole-2,3-dione

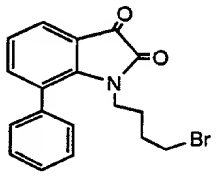


The title compound was prepared as described in Example 10 above except that 1-bromododecane was used.

^{1}H NMR : δ 0.6-0.7 (2H, m), 0.85 (3H, t), 0.9-1.4 (18H, m), 3.3 (2H, dd), 7.1 (1H, t), 7.3-7.5 (6H, m), 7.6 (1H, d)

Example 20

1-(4-Bromobutyl)-7-phenyl-1H-indole-2,3-dione



The title compound was prepared according to the process step described in the text from Page 7, line 34 to Page 8, line 5 of WO 94/29272 using 7-phenyl-1H-indole-2,3-dione and 1,4-dibromobutane.

^{1}H NMR : δ 0.7-0.8 (2H, m), 1.1-1.3 (4H, m), 1.6-1.8 (2H, m), 3.2-3.4 (4H, m), 7.1 (1H, t), 7.3-7.5 (6H, m), 7.6 (1H, d)

Example 21

Each of the compounds of Examples 1 to 20 was assessed for bactericidal activity against *M. tuberculosis* by measuring its minimum inhibitory concentration (MIC) in the "BACTEC" (trade mark) system developed by Becton-Dickinson Diagnostic Instrument Systems, Sparks, U.S.A., which is based on a radiometric principle whereby carbon dioxide released by the catabolism of ^{14}C-palmitate is spectrophotometrically detected and quantitated in arbitrary units of measurement referred to as growth index (GI) units.

Thus, "BACTEC" vials were inoculated with 0.1 ml of *M. tuberculosis* (final bacterial concentration, 1 x10^5 colony forming units per ml) and 0.1 ml of test compound in a range of concentrations. GI values were monitored until a value of ≥ 30 was achieved for the 1:100 dilution control.

For the purpose of this test, MIC is defined as the minimum concentration of test compound that effects a >95% inhibition of the culture in comparison to the undiluted control, when the control reaches a GI value of 999.

Endpoint determination (>99% inhibition) is based on a conventional 1% resistance cut-off, wherein the organism is considered resistant to a particular concentration of test compound if growth of greater than 1% of the bacterial population is observed. Thus, a comparison is made between growth of the organism in the presence of a pre-determined concentration of test compound and growth of the same organism diluted 1:100 in the absence of any test compound. The change in the GI values (ΔGI) is used to determine the endpoint susceptibility of the organism to the test compound. If the ΔGI of the 1:100 control is greater than the ΔGI in the presence of the test compound, then the concentration of test compound used is considered to be bactericidal (>99% inhibition) for the organism.

The MIC of the compounds of Examples 1 to 20 were determined for the following strains of *M. tuberculosis*:

H37Rv,

H37Ra,

1 clinical isolate susceptible to isoniazid, rifampicin, ethambutol and streptomycin [E:22/95; Estonia],

1 clinical isolate resistant to isoniazid [H:997/94; Honduras], 1 clinical isolate resistant to isoniazid and ethambutol [E:5/94; Estonia],

1 clinical isolate resistant to isoniazid and rifampicin [H:44/95; Honduras],

1 clinical isolate resistant to isoniazid and streptomycin [S:150/96; Sweden],

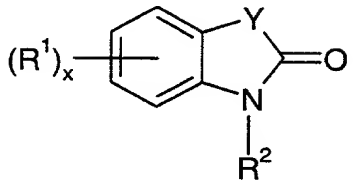
1 clinical isolate resistant to isoniazid, rifampicin and streptomycin [AA:063; Ethiopia],

3 clinical isolates resistant to isoniazid, rifampicin, streptomycin and ethambutol [P:24/95; Estonia, S:39/95; Nepal, S:42/95; China, H:1005/94; Honduras],

and were found in all cases to be less than or equal to 20 μg/ml. Therefore, the compounds of Examples 1 to 20 demonstrate effective bactericidal activity against the above strains of *M. tuberculosis* which include single- and multiple-drug resistant strains.

CLAIMS

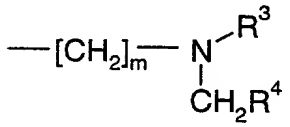
1. Use of a compound of general formula



(I)

wherein x represents 0 or 1, R^1 represents a 3- to 7-membered (hetero)cycloalkyl group or a phenyl group, Y represents a group CH_2 or >C=O, and R^2 represents either a C_1-C_{12} alkyl group optionally substituted by one or more halogen atoms,

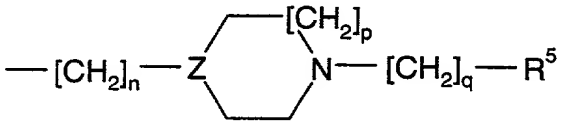
a group



(A)

wherein m represents an integer from 3 to 7, R^3 represents a C_1-C_6 alkyl group and R^4 represents a cyclohexyl or phenyl group optionally substituted by one or more substituents selected from the group consisting of a halogen atom, C_1-C_6 alkyl and C_1-C_6 alkoxy group,

or a group



(B)

wherein n represents an integer from 2 to 4, p and q independently represent an integer from 1 to 2, Z represents N or CH and R^5 represents a cyclohexyl or phenyl group optionally substituted by one or more substituents selected from the group consisting of a halogen atom, C_1-C_6 alkyl and C_1-C_6 alkoxy group,

or a pharmaceutically-acceptable salt or solvate thereof in the manufacture of a medicament for use in the treatment of a mycobacterial disease.

2. Use according to claim 1, wherein the mycobacterial disease is tuberculosis.

3. Use according to claim 1 or claim 2, wherein Y represents a group >C=O.

4. Use according to any one of claims 1 to 3, wherein R^1 represents a 5- to 7-membered (hetero)cycloalkyl group or a phenyl group.

5. Use according to claim 4, wherein R^1 is located in the 5- or 7-position.

6. Use according to any one of the preceding claims, wherein R^2 represents either a C_4-C_{12} alkyl group, a group (A) in which R^4 represents a phenyl group and m and R^3 are as defined in claim 1, or a group (B) in which n is 2, p is 1, q is 1, Z is N or CH and R^5 represents a phenyl group.

7. Use of a compound being:

5-Cyclohexyl-1-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-1H-indole-2,3-dione;

7-Cycloheptyl-1-[2-[4-(phenylmethyl)-1-piperazinyl]ethyl]-1H-indole-2,3-dione;

5-Cyclohexyl-1-(5-(N-ethyl-N-phenylmethylamino)pentyl)-1H-indole-2,3-dione;

5-Cyclohexyl-1,3-dihydro-1-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-2H-indol-2-one;

1-(4-(N-Ethyl-N-phenylmethylamino)butyl)-1H-indole-2,3-dione;

5-Phenyl-1-[2-[4-(phenylmethyl)-1-piperazinyl]ethyl]-1H-indole-2,3-dione;

7-Cyclopentyl-1-[2-[4-(phenylmethyl)-1-piperazinyl]ethyl]-1H-indole-2,3-dione;

5-(1-Piperidinyl)-1-[2-[4-(phenylmethyl)-1-piperazinyl]ethyl]-1H-indole-2,3-dione;

1-(4-Bromobutyl)-5-cyclohexyl-1H-indole-2,3-dione;

1-Nonyl-7-phenyl-1H-indole-2,3-dione;

1-Heptyl-7-phenyl-1H-indole-2,3-dione;

1-Octyl-7-phenyl-1H-indole-2,3-dione;

1-Decyl-7-phenyl-1H-indole-2,3-dione;

1-Undecyl-7-phenyl-1H-indole-2,3-dione;

1-Pentyl-7-phenyl-1H-indole-2,3-dione;

1-Butyl-7-phenyl-1H-indole-2,3-dione;

1-(2-Methylpropyl)-7-phenyl-1H-indole-2,3-dione;

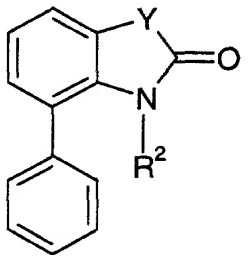
1-Hexyl-7-phenyl-1H-indole-2,3-dione;

1-Dodecyl-7-phenyl-1H-indole-2,3-dione; or

1-(4-Bromobutyl)-7-phenyl-1H-indole-2,3-dione;

or a pharmaceutically-acceptable salt or solvate thereof in the manufacture of a medicament for use in the treatment of a mycobacterial disease.

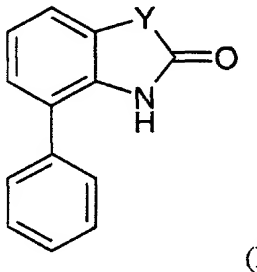
8. A compound of the general formula



(I')

wherein Y and R^2 are as defined in claim 1, or a pharmaceutically-acceptable salt or solvate thereof.

9. Process for the preparation of a compound of formula (I') as claimed in claim 8, which comprises reacting a compound of formula



(II)

in which Y is as defined in claim 1, with a compound of general formula (III), R^2-L, where L represents a leaving group and R^2 is as defined in claim 1, and optionally thereafter forming a pharmaceutically-acceptable salt or solvate thereof.

10. A pharmaceutical composition comprising a compound of formula (I'), or a pharmaceutically-acceptable salt or solvate thereof, as defined in claim 8 in association with a pharmaceutically-acceptable adjuvant, diluent or carrier.

11. A method of treating a patient suffering from, or at risk of, a mycobacterial disease, which comprises administering to the patient a therapeutically effective amount of a compound of formula (I), or a pharmaceutically-acceptable salt or solvate thereof, as defined in any one of claims 1 to 7.

ABSTRACT

NEW USE

The invention provides the use of certain isatin and oxindole derivatives in the preparation of a medicament for use in the treatment of mycobacterial disease.

Docket Number (Optional) R 1923-1P US

DECLARATION FOR PATENT APPLICATION

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled NEW USE the specification of which is attached hereto unless the following box is checked:

☒ was filed on 04 March 1999 as United States Application Number or PCT International Application Number SE99/00319 and was amended on _____ (if applicable).

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR § 1.56

I hereby claim foreign priority benefits under 35 U.S.C. § 119(a)-(d) or § 365(b) of any foreign application(s) for patent or inventor's certificate, or § 365(a) of any PCT International application which designated at least one country other than the United States, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or PCT international application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application(s)

			Priority Not Claimed
464/MAS/98	India	06 March 1998	☐
(Number)	(Country)	(Day/Month/Year Filed)	
9801370-9	Sweden	20 April 1998	☐
(Number)	(Country	(Day(Month/Year Filed)	

I hereby claim the benefit under 35 U.S.C. § 119(e) of any United States provisional application(s) listed below.

(Application Number)	(Filing Date)
(Application Number	(Filing Date)

I hereby claim the benefit under 35 U.S.C. § 120 of any United States application(s), or § 365(c) of any PCT International application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of 35 U.S.C. § 112.

I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR § 1.56 which became available between the filing date of the prior application and the national or PCT International filing date of this application.

(Application Number)	(Filing Date)	(Status -- patented, pending, abandoned)
(Application Number)	(Filing Date)	(Status -- patented, pending, abandoned)

I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith:

Edward V. Filardi, Reg. No. 25,757; Nels T. Lippert, Reg No. 25,888; Dimitrios Drivas, Reg. No. 32,218; Robert B. Smith, Reg. No. 28,538; Cecilia O'Brien Lofters, Reg. No. 33,434; David Bender, Reg. No. 35,445; John M. Genova, Reg. No. 32,224; Richard J. Sterner, Reg. No. 35,372; Hans-Peter G. Hoffmann, Reg. No. 37,352; Thelma C. Cleland, Reg.No. 40,948; Leslie Morioka, Reg. No. 40,304; John Scheibeler, Reg. No. 35,346; and Roy Waldron III, Reg. No. 42,208, all of the firm of WHITE & CASE Limited Liability Partnership, with offices at 1155 Avenue of the Americas, New York, New York 10036.

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Patent Department
1155 Avenue of the Americas
New York, NY 10036-2787

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believe to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Full name of sole or first inventor
(given name, family name) Ramachandran Janakiraman

First inventor's signature J Ramachandran Date: 11 March 1999

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